("Identical antigenic peptides can be bound to each ligand biding site of a molecular complex.") and at page 22, lines 27-29 ("A population of molecular complexes in which all ligand binding sites are found to identical antigenic peptides can also be bound to the cell.").

Claim 60 has been amended to recite "a lymphokine or other effector molecule which stimulates an immune response." This amendment is supported at page 21, lines 9-11: "Similarly, molecular complexes can be conjugated to molecules which stimulate an immune response, such as lymphokines or other effector molecules."

The amendments to the abstract are supported by the originally-filed abstract itself, as well as by page 19, lines 17-18, and page 22, lines 27-29, quoted above.

Objections to the Title and Abstract

The Office Action requested that the elected invention be added to the abstract and a new title descriptive of the elected invention be provided. Applicants have made the recommended amendments.

The Rejection of Claims 28-32 and 51-60 Under 35 U.S.C. § 112, second paragraph

Claims 28-32 and 51-60 stand rejected under 35 U.S.C. § 112, second paragraph. Applicants respectfully traverse this rejection.

Claims 32 and 56-58 are said to be unclear because they lack antecedent basis for "antigenic peptides of the population." This phrase has been deleted from claim 32. Claim 32 has been amended to recite that "an identical antigenic peptide is bound to each ligand binding site." A "ligand binding site" is recited in claim 28, on which claim 32 depends, thus providing antecedent basis. Claims 56-58 are dependent on claim 32 and recite "the antigenic peptides."

These claims now have proper antecedent basis.

Claims 56 and 57 are said to be ambiguous because the metes and bounds of "actively bound" and "passively bound" are allegedly not clear. Claims 56 and 57, however, would be clear to one of skill in the art because the recited types of binding are explained in the specification. The method of "active binding" is described in FIG. 3 of the specification and at page 19, lines 10-13: "Active binding can also be accomplished, for example, using alkaline stripping, rapid neutralization, and slow refolding of the molecular complex (see Figure 3 for a schematic)." The method of "passive binding" is described in the specification in the paragraph bridging pages 28 and 29:

> *Peptide Loading of Cells.* RMA –S and T2 cell lines are defective in antigen processing and express functionally "empty" class I MHC on their cell surface. These "empty" MHC molecules can be loaded with peptides using the following protocol (25). Cells (RMA-S, RMA-S L^d, T2, T2 L^d, T2 Kb, T2 Kbm3 or T2 K^{bm11}) are cultured at 27 °C overnight. The following morning, cells are cultured in the presence of various antigenic peptides (100 μM final concentration) or in the absence of peptides for an additional 1.5 hours at 27 °C and then incubated for one hour at 37 °C. RENCA cells were loaded with peptides by incubation with peptides (100 μM final concentration) for > hour at 37 °C.

Applicants are permitted to be their own lexicographers. *Hormone Research Foundation Inc. v. Genentech Inc.*, 904 F.2d 1558, 15 U.S.P.Q.2d (BNA) 1039 (Fed. Cir. 1990). Provided with these teachings in the specification, the metes and bounds of "actively bound" and "passively bound" are clear.

Claim 60 is said to be indefinite because the metes and bounds of "a molecule which stimulates an immune response" are allegedly not clear. Molecules which stimulate an immune response are defined at page 21, lines 9-11 of the specification: "Similarly, molecular complexes can be conjugated to molecules which stimulate an immune response, such as lymphokines or

other effector molecules." Claim 60 has been amended to recite "a lymphokine or other effector molecule which stimulates an immune response."

Finally, the paragraph bridging pages 22-23 is said to be unclear. This paragraph is discussed in connection with the rejection under 35 U.S.C. § 112, first paragraph, as it does not relate to claim clarity but to specification clarity.

Applicants respectfully request withdrawal of the rejection.

The Rejection of Claims 28-32 and 51-60 Under 35 U.S.C. § 112, first paragraph

Claims 28-32 and 51-60 stand rejected under 35 U.S.C. § 112, first paragraph, as not enabled. Applicants respectfully traverse the rejection.

The Office Action asserts that the specification does not teach how to make a composition comprising a cell to which molecular complexes are bound, including what part of the molecular complex is bound to the cell, or how to use the composition. The specification teaches how to make the claimed compositions in the paragraph bridging pages 22-23:

> Molecular complexes of the invention can be bound to the surface of a cell, such as a dendritic cell. A population of molecular complexes in which all ligand binding sites are bound to identical antigenic peptides can also be bound to the cell. Binding can be accomplished by providing the fusion protein of the molecular complex with an amino acid sequence which will anchor it to the cell membrane and expressing the fusion protein in the cell or can be accomplished chemically, as is known in the art.

The quoted paragraph teaches two options for binding molecular complexes to a cell: chemical linkage or use of an anchoring amino acid sequence fused to fusion proteins of the molecular complex.

Chemical linkage of proteins to cells was well-known in the art at the priority date of this

application (March 28, 1996). For example, Lisanti *et al.*, "A glycophospholipid membrane anchor acts as an apical targeting signal in polarized epithelial cells," *J. Cell. Biol. 109*, 2145-56, 1989 (Attachment 1), teaches linkage of proteins to cell membranes via a glycosylated form of phosphatidylinositol.[1] *See also* Low, *FASEB J. 3*, 1600-08, March 1989 (Attachment 2). Methods of chemically linking two proteins together also were well known and could have been used to link fusion proteins of the molecular complexes to cell surface proteins. *See* Pain & Surolia, *J. Immunol. Methods 40*, 219-30, 1981 (Attachment 3), Deelder & de Water, *J. Histochem. Cytochem. 29*, 1273-80, 1982 (Attachment 4); and Carlsson *et al.*, *Biochem. J. 173*, 723-37, 1978 (Attachment 5).

Anchoring amino acid sequences also were well known. For example, U.S. Patent 5,342,924 (filed July 3, 1993 and issued August 30, 1994) teaches that:

> The amino acid sequences of ten membrane-bound immunoglobulins from several species have been previously determined by other groups. See Ishida, N. et al., EMBO J., 1: 1117 (1982); Steen, M. L. et al., J. Mol. Biol., 177: 19-32 (1984); Rogers, J. et al., Cell, 26: 19-27 (1981); Yamawaki-Kataoka, Y. et al., Proc. Natl. Acad. Sci., MSA, 79: 2008-2012 (1982); Kamaromy, M. et al., Nuc. Acids Res., 11: 6775-6785 (1983); Rogers, J. et al., Cell, 20: 303-312 (1980); Bernstein, K. E., J. Immunol. 132: 490-495 (1984); Cheng, H. et al., Nature, 296: 410-415 (1982). These sequences indicate certain common features of the membrane anchoring peptides.

Col. 3, lines 31-42. *See also* Wang *et al.*, *DNA 8*, 753-58, 1989 (Attachment 6), and Dubel *et al.*, *Gene 128*, 97-101 (June 15, 1993) (Attachment 7), which teach vectors that can be used for cell surface display of proteins. Any such methods could have been used by those skilled in the art to bind molecular complexes to a cell, such as a dendritic cell.

The Office Action asserts it is unclear "if the claims intend for the molecular complex to

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1 Full texts of the publications in Attachments 1-7 will be provided in a supplemental response.

be bound to any cell by means of the ligand binding sites or via other parts of the complex such as the various immunoglobulin domains." Page 4, lines 10-12. The specification contemplates binding via other parts of the complex, such as the various immunoglobulin domains. Thus, binding does not occur by means of the ligand binding site, as the ligand binding site is used to bind antigenic peptides. See page 22, lines 27-29: "A population of molecular complexes in which all ligand binding sites are bound to identical antigenic peptides can also be bound to the cell."

The Office Action also asserts that the specification does not teach how to use compositions comprising such cells. When assessing whether a specification provides an enabling description, all the evidence must be considered as a whole. M.P.E.P. § 2164.05. The evidence includes the teachings of the specification. The present specification teaches diagnostic and therapeutic uses for molecular complexes that are equally applicable to compositions in which molecular complexes are bound to cells. For example, the specification teaches that "molecular complexes of the invention can be used diagnostically, to label antigen-specific cells *in vitro* or *in vivo*." Page 19, lines 19-20. Cells which bear molecular complexes on their surface can similarly be used for such detection methods. Cells of the claimed compositions can be used in the cell separation methods described on page 20, first paragraph.

The specification explicitly teaches that molecular complexes can be bound to the surface of dendritic cells. Page 22, lies 26-27. It is well-known in the art that dendritic cells are antigen-presenting cells. *See* Abbas *et al.*, CELLULAR AND MOLECULAR IMMUNOLOGY, 3d ed., page 240 (Attachment 8). Use of dendritic cells to which molecular complexes are bound and in which each molecular complex has an identical antigenic peptides bound to its ligand binding sites can be used to present such antigens to T cells. Therapeutic use of presenting antigens to T cells is

taught, *inter alia*, at page 21, line 22, to page 22, line 25.

Considered as a whole, the specification teaches uses for the claimed compositions of cells as well as how to make the compositions. Applicants respectfully withdrawal of the rejection.

Respectfully submitted,

6-26-02
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Appendix 1. Version of the amended claims and paragraph, with markings to show changes made

32. (amended) The composition of claim 28 wherein a population of the molecular complexes is bound to the cell, wherein [the antigenic peptides of the population are identical] an identical antigenic peptide is bound to each ligand binding site.

60. (amended) The composition of claim 28 wherein the molecular complex is conjugated to a lymphokine or other effector molecule which stimulates an immune response.

Page 63:

Compositions comprising a cell in which a molecular complexe with high affinity for its cognate ligand is bound to the surface of the cell are provided. To form the molecular complexes, extracellular [Extracellular] domains of transmembrane heterodimeric proteins, particularly T cell receptor and major histocompatibility complex proteins, can be covalently linked to the heavy and light chains of immunoglobulin molecules [to provide soluble multivalent molecular complexes with high affinity for their cognate ligands]. The molecular complexes can be used, *inter alia*, to detect and regulate antigen-specific T cells and as therapeutic agents for treating disorders involving immune system regulation, such as allergies, autoimmune diseases, tumors, infections, and transplant rejection. Optionally, identical antigenic peptides can be bound to each ligand binding site of a molecular complex.